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## STOMACH

# Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia

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**Background and aims:** Dietary fat plays a role in the pathophysiology of symptoms in functional dyspepsia (FD). In healthy subjects, cognitive factors enhance postprandial fullness; in FD patients, attention increases gut perception. We hypothesised that the information given to patients about the fat content of a meal would affect dyspeptic symptoms.

**Methods:** Fifteen FD patients were each studied on four occasions in a randomised double blind fashion. Over two days they ingested a high fat yoghurt (HF) and over the other two days a low fat yoghurt (LF). For each yoghurt, the patients received the correct information about its fat content on one day (HF-C, LF-C) and the opposite (wrong) information on the other day (HF-W, LF-W). Dyspeptic symptoms, plasma cholecystokinin (CCK) concentrations, and gastric volumes were evaluated.

**Results:** Both the fat content and information about the fat content affected fullness and bloating scores—both were higher after HF-C compared with LF-C, and LF-W compared with LF-C, with no differences between HF-C and HF-W. Nausea scores were higher after HF compared with LF, with no effect of the information about fat content. No differences between discomfort and pain scores were found between study conditions. Plasma CCK and gastric volumes were greater following HF compared with LF, with no effect of the information given to the patients. All differences are  $p < 0.05$ .

**Conclusions:** Cognitive factors contribute to symptom induction in FD. Low fat foods may also elicit symptoms if patients perceive foods as high in fat, while CCK and gastric volumes do not appear to be affected by cognitive factors.

There is growing evidence that nutrients, particularly fat, play an important role in the pathophysiology of functional dyspepsia (FD).<sup>1–4</sup> Many patients with FD report that their symptoms are exacerbated after ingestion of foods containing fat. Ingestion of a high fat soup induces more severe symptoms than the same soup without fat.<sup>3</sup> Moreover, duodenal fat infusion results in a dose related increase in the severity of dyspeptic symptoms in these patients.<sup>5</sup> This effect appears to be specific for fat as only duodenal infusion of fat, but not glucose, induces the symptomatic response.<sup>6</sup>

A number of mechanisms may, at least in part, mediate the effects of fat on dyspeptic symptoms. Fat may act indirectly via changes in gastrointestinal motility, for example through an increase in proximal gastric relaxation.<sup>7</sup> However, our data suggest that duodenal lipid induces symptoms independently of any changes in proximal gastric motor function;<sup>5</sup> increasing the dose of duodenal fat is associated with an increase in the severity of symptoms while the increase in proximal gastric volume is not related to the fat dose. In contrast, fat digestion is required for the induction of "dyspeptic" symptoms in healthy subjects,<sup>9</sup> and the beneficial effect of the cholecystokinin (CCK)-A receptor antagonist dexloxiglumide on symptoms induced by duodenal fat infusion during gastric distension in patients with FD suggests that CCK is also involved.<sup>5</sup> As these factors do not entirely explain the symptoms, other factors need to be taken into consideration. These include other gastrointestinal peptides and psychological factors, among others; their contribution to symptom development after food ingestion, particularly in relation to fat, in FD is unknown.

Cognitive factors play a role in appetite regulation; in healthy subjects, a nutrient containing soup induces a greater perception of fullness when subjects are informed of the nature of the soup compared with the control condition in

which the subjects are not explicitly given this information.<sup>10</sup> In patients with FD, both attention (due to anticipatory knowledge) and distraction (by performance of a mental task) modulate perception of duodenal distension; attention increases and distraction attenuates gut perception.<sup>11</sup> It is therefore conceivable that FD patients respond with symptoms to certain foods as a result of a previous negative learning experience or information they have received; the possibility that even foods with a low fat content may increase symptoms if patients perceive them as high in fat has not been evaluated.

The aim of our study was therefore to evaluate in patients with FD the role of cognitive factors on symptom induction, proximal gastric motor function, and plasma CCK concentrations in response to high fat and low fat yoghurts. We investigated the hypothesis that the information given to the subjects as to the fat content of the yoghurts would affect the severity of symptoms.

## SUBJECTS AND METHODS

### Subjects

Fifteen patients (nine women, six men; aged 24–56 years (median 42)) with FD participated in the study. All patients were of normal body weight for height (body mass index 22.8 (0.9) kg/m<sup>2</sup>), non-smokers, and did not take any medication during the course of the study. The study was carried out with the approval of the ethics committee at the University Hospital Zürich. All patients gave their informed written consent prior to participation. Patients were recruited by advertisement in local newspapers describing the symptomatic

**Abbreviations:** FD, functional dyspepsia; CCK, cholecystokinin; VAS, visual analogue scale; MDP, minimal distending pressure

criteria required for entry into the study. In a telephone interview, patients were selected for further investigation depending on the presence and severity of symptoms. Patients had at least three of the following symptoms for more than six months of at least a moderate severity: postprandial fullness/early satiety, bloating, epigastric pain, and nausea/vomiting. Severity was scored on a 0–3 scale with 0 representing “symptoms not experienced”, 1 “slight symptoms, but not bothering”, 2 “moderate symptoms, bothering, but not impairing daily activities”, and 3 “severe symptoms, impairing daily activities”. Patients who had previously undergone gastrointestinal surgery or were on medications that could not be discontinued for the duration of the study were not included. Each patient underwent laboratory tests, upper gastrointestinal endoscopy, abdominal ultrasound, a  $^{13}\text{C}$ -urea breath test for *Helicobacter pylori* status, and a  $\text{H}_2$  breath test to assess lactose intolerance. If all investigations were negative, patients were admitted into the study. Each subject was required to visit the laboratory once before the start of the study. During this visit, subjects were familiarised with the requirements of the study, the gastric (barostat) tube, the study procedures, and the symptom questionnaires.

## Methods

### Test meals

Two yoghurts (weight 300 g each) were used as test meals. The low fat yoghurt (LF) consisted of 150 g fat free yoghurt, 75 g low fat milk, and 75 g raspberries (143 kcal, energy from fat 8.1% (1.3 g), from carbohydrate 63.6% (21.6 g), and from protein 28.3% (9.8 g)). The high fat yoghurt (HF) consisted of 75 g whole fat yoghurt, 75 g cream, 75 g whole fat milk, and 75 g raspberries (330 kcal, energy from fat 66.6% (23.6 g), from carbohydrate 23.5% (18.5 g), and from protein 9.9% (8.0 g)). The ingredients were blended with an electric mixer to obtain a thick consistency for both yoghurts. Both yoghurts were appetising, and of similar taste, consistency, and colour. Prior to administration to patients, samples of both yoghurts were given to 16 healthy subjects in a randomised order and immediately following each other to test for palatability and whether subjects noticed any differences, including sweetness, fat content, taste, or acidity between the two yoghurts. All subjects rated both shakes as very palatable, and five subjects did not notice a difference between the yoghurts. The remaining 11 subjects indicated that the yoghurts differed with regard to their sweetness (seven subjects), fat content (two subjects), taste (eight subjects), and acidity (five subjects). None of the subjects was able to correctly assign fat content to the appropriate yoghurt.

### Gastric tube and barostat

Changes in gastric volume in response to the test meals were evaluated in seven (four women, three men) of the 15 patients (the other eight patients did not tolerate the barostat tube, as revealed during the prestudy visit). For this purpose, each patient was intubated with a single lumen tube (OD 3.5 mm, ID 2.8 mm; Tygon Tubing, Upchurch Scientific, Oak Harbor, Washington, USA), which had a flaccid thin walled polyethylene bag (capacity 1100 ml) attached to its distal end. The proximal end of the tube was connected via a three way tap to the measurement and balloon ports of a gastric barostat (Distender Series II; G&J Electronics Inc., Willowdale, Ontario, Canada). Functioning of the barostat has been described in detail elsewhere.<sup>7</sup> In brief, it is capable of measuring changes in gastric volume at a fixed pressure. Thus when the gastric wall relaxes, air is injected into the gastric bag to maintain the pressure while air is withdrawn when the stomach contracts. The barostat bag was positioned

in the fundus of the stomach, as described previously.<sup>2</sup> The bag was unfolded by inflating it with air, positioned in the fundus by gently pulling the tube back until its passage was restricted by the lower oesophageal sphincter, and then pushed back in by 3 cm. The tubes were then secured to the side of the face. Subjects tolerated the tubes well and did not sense the empty bag in the stomach.

### Blood sampling

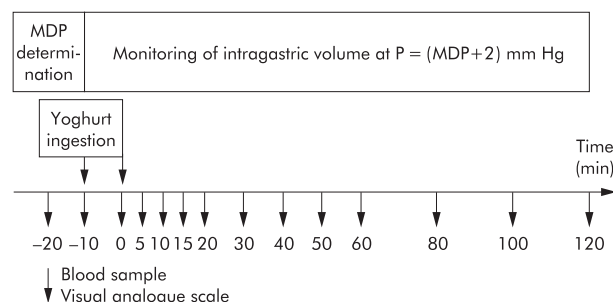
Venous blood samples were taken repeatedly throughout the study (fig 1) to determine plasma levels of CCK at baseline and following meal ingestion. Samples were collected in chilled EDTA tubes, centrifuged at 2°C for 15 minutes, and stored at –70°C until extraction. Plasma CCK was determined by a sensitive and specific commercially available radioimmunoassay kit (Euro-Diagnostica BV, Arnhem, the Netherlands). Cross reactivity with sulphated gastrins was 0.5%, while cross reactivity with unsulphated gastrins was <0.01%. The sensitivity of the assay was 0.3 pmol/l with a confidence limit of 2 SD. The coefficients of variation were 5.5% at 4.4 pmol/l and 2.0% at 20.6 pmol/l for the intra-assay variation, and 13.7% at 4.2 pmol/l and 4.1% at 20.6 pmol/l for interassay variation.

### Assessment of symptoms

The severity of postprandial fullness, bloating, epigastric discomfort, pain, and nausea was assessed by means of previously validated visual analogue scales (VAS)<sup>12</sup> at baseline and repeatedly after meal ingestion (fig 1). The VAS was a 10 cm line, with 0 representing “sensation/symptom not present” and 10 “sensation/symptom extremely strong/uncomfortable”.

### Experimental protocol

Each patient was studied on four separate occasions. All studies were carried out in the morning after an overnight fast, 5–10 days apart, and each study took approximately three hours. Patients who underwent the barostat study were intubated, and the minimal distending pressure (MDP) was determined first by raising intrabag pressure with the barostat in steps of 1 mm Hg/min. MDP has previously been defined as the pressure that is necessary to overcome intra-abdominal pressure resulting in a bag volume of at least 30 ml. Intra-gastric pressure was set at 2 mm Hg above MDP



**Figure 1** Experimental protocol. Patients ingested a high fat or a low fat yoghurt (each on two occasions; on one occasion patients were correctly informed about the fat content of the yoghurt—that is, “this is a high fat yoghurt” or “this is a low fat yoghurt”, respectively—while on the other occasion subjects were given the wrong information—that is, “this is a low fat yoghurt” or “this is a high fat yoghurt”, respectively). Patients (n = 15) rated dyspeptic symptoms (including bloating, fullness, nausea, and discomfort, pain) at regular intervals and blood samples for determination of plasma cholecystokinin concentrations were taken at the same time points. In addition, changes in gastric volume in response to the four study conditions were recorded in seven of the 15 patients using an electronic barostat. MDP, minimal distending pressure (“baseline” pressure).

( $t = -20$  minutes) and the corresponding volume was monitored until a stable recording was obtained for at least 10 minutes (baseline,  $t = -10$  minutes). Then patients ingested the test meal within 10 minutes (end of yoghurt ingestion:  $t = 0$  minutes), each yoghurt on two occasions. The two occasions differed with regard to the information the patients received about the composition of the yoghurt. On one occasion, patients received the correct information regarding the fat content of the yoghurt (that is "you will now be invited to eat a high fat yoghurt" in the case of the high fat yoghurt (condition HF-C) or "you will now be invited to eat a low fat yoghurt" in the case of the low fat yoghurt (condition LF-C)); on the other occasion they received the wrong information (that is, "you will now be invited to eat a low fat yoghurt" in the case of the high fat yoghurt (condition HF-W) or "you will now be invited to eat a high fat yoghurt" in the case of the low fat yoghurt (condition LF-W)), in a standardised fashion, and patients were presented with the empty containers of the ingredients. In the seven patients with the barostat tube in place, monitoring of gastric volume continued for two hours, and in all patients blood samples were drawn and symptoms assessed at regular intervals—that is, fasting (baseline) samples at  $t = -20$ , and  $-10$  min, post-meal samples immediately after meal ingestion ( $t = 0$  min), and then every five minutes for the first 20 minutes, every 10 minutes for the subsequent 40 minutes, and every 20 minutes for the final 60 minutes (until  $t = 120$  minutes).

### Data analysis

Changes in gastric volume during the different study conditions were calculated by averaging the volume readings obtained during the baseline period (at MDP +2 mm Hg) and during consecutive 10 minute periods following meal ingestion. Data obtained at  $t = -20$  and  $-10$  minutes for the different parameters (VAS scores, plasma CCK concentrations, gastric volumes) were then averaged to obtain a baseline value. As these values varied slightly between study conditions, they were adjusted using study day LF-C as a reference, and then entered into the analysis.

### Statistical analysis

Data were analysed using repeated measures analysis of variance (two way ANOVA) with time and treatments as factors. A  $p$  value  $<0.05$  was considered statistically significant. Data are presented as means (SEM).

## RESULTS

### Symptomatic responses

#### Fullness (fig 2A)

Scores for fullness increased following ingestion of all yoghurts ( $p = 0.0001$ ). Both the fat content of the yoghurt

and the information given to the subjects as to the fat content of the yoghurts tended to affect ratings for fullness ( $p = 0.067$ ). Scores for fullness were higher following ingestion of the high fat yoghurt compared with the low fat yoghurt (HF-C  $\nu$  LF-C;  $p = 0.041$ ). The information given to subjects as to the fat content of the yoghurt markedly affected scores for fullness following ingestion of the low fat yoghurt; subjects felt significantly more full when told that the yoghurt was high in fat (LF-C  $\nu$  LF-W;  $p = 0.013$ ) while the information given to the subjects did not increase the severity of fullness following ingestion of the high fat yoghurt any further (HF-C  $\nu$  HF-W;  $p = 0.803$ ). In contrast, there was no difference in scores for fullness between the high fat yoghurt when subjects were told it was low in fat and the low fat yoghurt when subjects were told it was high in fat (HF-W  $\nu$  LF-W;  $p = 0.474$ ).

#### Bloating (fig 2B)

Bloating scores increased following ingestion of all yoghurts ( $p = 0.0001$ ). Both the fat content of the yoghurt and the information given to the subjects as to the fat content of the yoghurts affected ratings for bloating ( $p = 0.038$ ). Scores for bloating were higher following ingestion of the high fat yoghurt compared with the low fat yoghurt (HF-C  $\nu$  LF-C;  $p = 0.042$ ). The information given to subjects as to the fat content of the yoghurt affected scores for bloating following ingestion of the low fat yoghurt; subjects tended to feel more bloated when told that the yoghurt was high in fat (LF-C  $\nu$  LF-W;  $p = 0.056$ ). In contrast, the information given to the subjects did not increase the severity of bloating following ingestion of the high fat yoghurt any further (HF-C  $\nu$  HF-W;  $p = 0.412$ ).

#### Nausea (fig 2C)

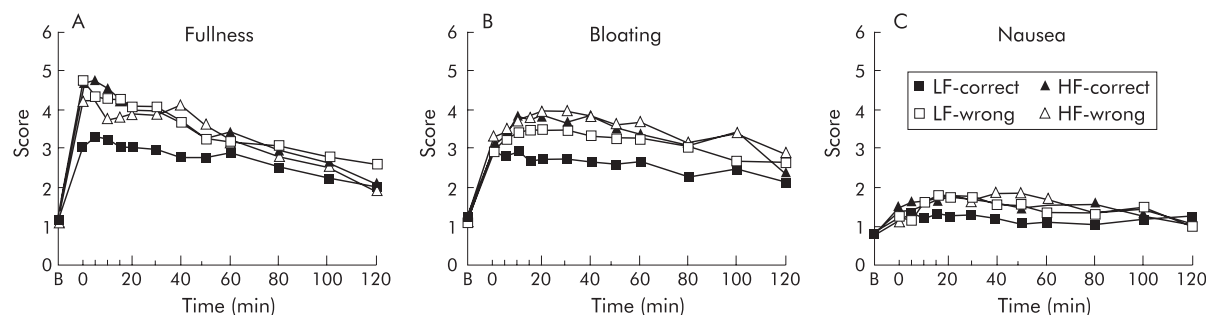
Ratings for nausea were slightly higher following ingestion of the high fat yoghurt when subjects were informed that the yoghurt was high in fat compared with the low fat yoghurt when subjects were informed that the yoghurt was low in fat (HF-C  $\nu$  LF-C;  $p = 0.012$ ). In contrast, the information given to subjects did not affect nausea ratings within the type of yoghurt (HF-C  $\nu$  HF-W ( $p = 0.716$ ); LF-C  $\nu$  LF-W ( $p = 0.176$ )).

#### Discomfort

Scores for discomfort increased following ingestion of all yoghurts ( $p = 0.001$ ). However, there was no difference in scores between the four study conditions ( $p = 0.165$ ).

#### Pressure/pain

Pain scores increased only slightly following ingestion of all yoghurts ( $p = 0.001$ ) but there was no difference in scores between the four study conditions ( $p = 0.424$ ).



**Figure 2** Scores for fullness (A), bloating (B), and nausea (C) following ingestion of a high fat (HF) or a low fat (LF) yoghurt with patients receiving either the correct (that is, "this is a HF yoghurt" or "this is a LF yoghurt", respectively) or the wrong (that is, "this is a LF yoghurt" or "this is a HF yoghurt", respectively) information with regard to the fat content of the yoghurts. Data are means of  $n = 15$  patients.



### Plasma CCK concentrations

Both yoghurts increased plasma CCK concentrations ( $p = 0.0001$ ) but the high fat yoghurt increased plasma CCK more than the low fat yoghurt (HF-C v LF-C;  $p = 0.036$ ). Plasma CCK concentrations did not differ whether subjects were given the correct or wrong information as to the fat content of the yoghurt, although levels tended to be higher during condition HF-correct (HF-C) compared with condition HF-wrong (HF-W) (fig 3).

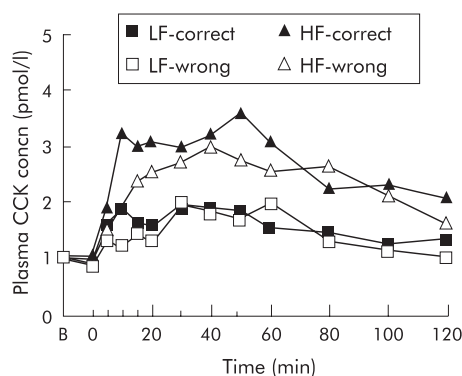
### Gastric volume changes

Gastric volumes increased following ingestion of both yoghurts ( $p = 0.001$ ), except for condition LF-C (fig 4). In addition, gastric volumes were greater following ingestion of the high fat yoghurt compared with the low fat yoghurt (HF-C v LF-C;  $p = 0.012$ ). The information about the fat content of the yoghurt did not significantly affect gastric volumes.

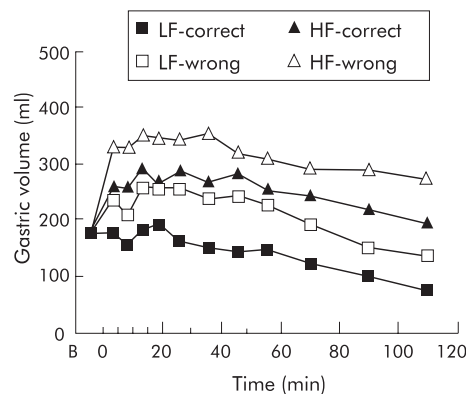
## DISCUSSION

Our data demonstrate that: (1) cognitive factors contribute to exacerbation of symptoms, particularly fullness, in FD, (2) symptoms after ingestion of a low fat meal are particularly affected by cognitive factors, while (3) plasma CCK concentrations and gastric volumes appear to be unaffected by cognitive factors. In addition, our data confirm previous reports that a high fat meal induces greater dyspeptic symptoms and results in greater plasma CCK concentrations and gastric volumes than a low fat meal.

The most interesting and novel finding of our study is that some of the most frequent dyspeptic symptoms, fullness and bloating, are exacerbated not only by ingestion of a meal high in fat but also by a meal that is *perceived* by the patients as high in fat. This has not been demonstrated previously and indicates that the situation with regard to the role of fat in dyspeptic symptom induction is more complex than assumed previously.<sup>6</sup> Our data therefore suggest that at least two factors are involved in the induction of dyspeptic symptom related to fat: (1) the *actual* fat content of the meal—symptoms were more severe following the high fat yoghurt compared with the low fat yoghurt; and (2) the *perceived* fat content of the meal—patients associate fat ingestion with the occurrence of symptoms and, as a result, experience them. The mechanism(s) underlying this phenomenon is unknown. It has been described previously that anticipatory knowledge of gut distension enhances perception of this stimulus in patients with FD,<sup>11</sup> and awareness of the nutrient content of a



**Figure 3** Plasma cholecystokinin (CCK) concentrations following ingestion of a high fat (HF) or low fat (LF) yoghurt with patients receiving either the correct (that is "this is a HF yoghurt" or "this is a LF yoghurt", respectively) or the wrong (that is, "this is a LF yoghurt" or "this is a HF yoghurt", respectively) information with regard to the fat content of the yoghurts. Data are means of  $n = 15$  patients.



**Figure 4** Gastric volumes following ingestion of a high fat (HF) or low fat (LF) yoghurt with patients receiving either the correct (that is, "this is a HF yoghurt" or "this is a LF yoghurt", respectively) or the wrong (that is, "this is a LF yoghurt" or "this is a HF yoghurt", respectively) information with regard to the fat content of the yoghurts. Data are means of  $n = 7$  patients.

soup increases the feeling of fullness in healthy subjects.<sup>10</sup> These previous findings indicate that the occurrence of symptoms in patients with FD may perhaps be the result of some form of conditioning due to the experience of exacerbation of symptoms after ingestion of fatty foods in the past. These previous findings also indicate that cognitive factors influencing perception related to food ingestion occur in both healthy subjects and in patients with FD. The substantial effect of placebo treatment on symptom improvement of up to 50%,<sup>13 14</sup> which in some studies was similar to the effect of the drug under study,<sup>13</sup> is well documented in patients with FD. This effect appears to occur independently of any changes in gastrointestinal motility or gastric perception,<sup>15</sup> and a reduction in anxiety, as a result of the patient's belief that the treatment will relieve symptoms, has been discussed as a possible underlying mechanism.<sup>15</sup> It is therefore conceivable that this effect is reversed in a situation in which patients are confronted with a food, which they perceive as having detrimental effects on their symptoms, as in our study. Certainly, further studies are required to investigate these findings in more detail as an understanding of the role of cognitive factors may potentially provide opportunities for novel therapeutic approaches. In contrast, symptoms following the high fat yoghurt were not affected by the information about the fat content. This may indicate that the fat contained in the yoghurt per se had a dominant independent effect on symptoms that could not be further modulated by cognitive factors—that is, the cognitive influence was weaker than the effect of fat.

The observation that patients with FD may also experience symptoms after ingestion of low fat foods as a result of cognitive influences, and not only after ingestion of foods containing fat, raises the question as to the value of dietary modification—for example, the adoption of a low fat diet—in the management of dyspeptic symptoms apparently related to fat ingestion. This may be particularly relevant in patients in whom cognitive effects are suspected to have a major influence on symptoms, and suggests that cognitive-behavioural training may be a therapeutic strategy in patients that complain of symptoms associated with eating, or ingestion of specific foods, but are refractory to dietary modification.

In considering underlying pathophysiological mechanisms, studies in both humans and experimental animals have demonstrated marked effects of somatic and mental stress and anxiety on gut motility and visceral perception.<sup>11 16–20</sup> In

addition, it has been suggested that plasma concentrations of some gastrointestinal peptides, including CCK and somatostatin, are significantly more elevated in response to a stressful interview in patients with FD compared with healthy subjects.<sup>21</sup> We were unable to find differences in postprandial plasma CCK concentrations or gastric volumes (as a measure of gastric relaxation) in relation to the information about fat content. Our data indicate that CCK is not involved in exacerbation of symptoms by cognitive influences. While plasma CCK concentrations tended to be higher, although not statistically significant, when patients were informed that the yoghurt was high in fat, the severity of symptoms did not differ between the two high fat study conditions. Therefore, our data do not provide evidence that CCK is involved in symptom induction related to the perceived fat content of a meal. The role of other gastrointestinal peptides or stress related hormones, including corticotropin releasing factor,<sup>22</sup> may warrant further investigation. In addition, while our data suggest that proximal gastric relaxation does not play a role in the exacerbation of symptoms by cognitive influences, the lack of a statistically significant difference may be the result of a type 2 error and warrants further investigation.

In conclusion, our data provide evidence for a role of cognitive factors in symptom induction in functional dyspepsia, particularly after ingestion of low fat meals if patients perceive them as containing high fat quantities, while CCK and gastric volumes do not appear to be affected significantly by cognitive factors. Our findings may have important clinical implications and strongly suggest that cognitive influences need to be taken into consideration in the treatment of functional dyspepsia.

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# PostScript

## LETTERS

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### Ghrelin and *Helicobacter pylori*

We read with interest the article by Nwokolo *et al* reporting raised serum ghrelin levels following *Helicobacter pylori* eradication (Gut 2003;52:637-40). There are some exceptions to the interpretation of the data that we would take.

The authors state that the increase in ghrelin levels seen in their study "lends support to the view that ghrelin could be involved in the long term regulation of body weight". While there is growing evidence to support this in the literature,<sup>1-3</sup> this study does not present any such data and is not methodologically geared towards addressing this question. The proposal that eradication of *H pylori* leads to an increase in ghrelin levels, which in turn leads to an increase in obesity, is also without foundation. The only known situation in which hyper-ghrelinemia is associated with obesity is in Prader-Willi syndrome.<sup>4</sup> In all other studies ghrelin levels correlate inversely with measures of body adiposity, and are altered in a compensatory manner by changes in body weight.<sup>5</sup> To suggest therefore that *H pylori* eradication leads to a hyper-ghrelinemic state that drives increased appetite is not physiologically feasible as any transient appetite increase would be expected to be countered by any increase in adiposity, which in turn would suppress ghrelin levels.

The authors' proposal that "children with *H pylori* may have relatively low ghrelin concentrations contributing to growth retardation" is also without foundation. A recent study has shown *H pylori* status to have no effect on ghrelin levels.<sup>6</sup> The role of ghrelin on the growth of children remains unclear. Ghrelin is an endogenous ligand to the growth hormone secretagogue receptor (GHS-R), and potentially stimulates growth hormone release. It may indeed have a role to play in growth, as in patients with a genetic growth hormone releasing hormone deficiency nocturnal enhancement of growth hormone secretion remains,<sup>7</sup> an effect that may be mediated by ghrelin.

One other proposal of the authors is that *H pylori* eradication increases 24 hour gastric acidity by a ghrelin dependent mechanism. While central and peripheral ghrelin

administration has been shown to increase stomach acidity when given to rats,<sup>8</sup> data are lacking in humans. The small but statistically significant increase in acidity seen here would be expected after *H pylori* eradication, and is likely to be secondary to parietal cell recovery following resolution of inflammation. The suggestion that hypergastrinaemia leads to lower ghrelin levels, and vice versa, is not supported in the literature.<sup>9</sup>

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### Authors' reply

We would like to draw the attention of Drs Murry and Emmanuel to the objectives set out clearly in the introductory section of our paper.

Our study was not designed to address the question of whether ghrelin is involved in long term regulation of body weight. Furthermore, the duration of the study was too short to see any change in body mass index. More importantly, waist circumference would be a better anthropometric measure of change in body fat composition supported by sequential dual energy x ray absorptiometry or magnetic resonance imaging. The results of our study were unexpected and there was nothing in the literature that gave us forewarning. We would have designed the study to follow up the subjects for at least one year, monitoring their plasma ghrelin, and assessing changes in body composition using the techniques described above.

The authors refer to "physiological feasibility" and thereby miss the point that *Helicobacter pylori* infected stomachs exhibit distortion of normal physiological mechanisms. For

example, the tight reciprocal relationship between gastrin and intragastric acidity seen in *H pylori* negative subjects is modified in *H pylori* positive subjects. We believe that a *H pylori* infected stomach produces less ghrelin, leading to decreased appetite and food intake. The physiological response should be that the resulting weight loss leads to a compensatory increase in ghrelin, increased appetite, and weight gain, and so on. We believe that this "physiological" mechanism is altered by the presence of *H pylori*, possibly by resetting a putative "ghrelin thermostat" at a lower level, allowing thinness and hypo-ghrelinemia to occur together. Proof will come only from further experimentation.

The authors cite a study comparing spot measurements of plasma ghrelin in women with and without *H pylori* gastritis;<sup>1</sup> this does not amount to a robust challenge to our hypothesis on *H pylori*, ghrelin, and children. The authors repeat the widely held although unproven belief that the increase in intragastric acidity after *H pylori* cure can be attributed to recovery of parietal cells from inflammation. They ignore our observation of a positive correlation between ghrelin and 24 hour intragastric acidity. We accept that the relationship between gastrin and ghrelin is unproven in humans but this emphasises the paucity of human data and the need for more studies.

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- Gokcel A, Gumurdulu Y, Kayaselcuk F, *et al*. *Helicobacter pylori* has no effect on plasma ghrelin levels. *Eur J Endocrinol* 2003;148:423-6.

### *Helicobacter pylori*, ghrelin, and obesity

Nwokolo *et al* have demonstrated that following eradication of *Helicobacter pylori* from asymptomatic patients, plasma ghrelin "increases profoundly" (Gut 2003;52:637-40). Although we find these results interesting, we cannot agree with the conclusion that this may be causally linked to epidemiological observations of the rising incidence of obesity and oesophageal adenocarcinoma in Western populations. In particular, the present study in fact demonstrates that after *H pylori* eradication, ghrelin merely returns to levels detected in non-obese control patients using the same hormone assay.<sup>1</sup> It would seem likely that *H pylori* infection, leading to oxyntic gland atrophy,<sup>2</sup> is associated with at most a mild suppression of plasma ghrelin, which recovers after treatment. This seems unlikely to have a profound effect on calorie intake, particularly as obese patients have a lower mean plasma ghrelin concentration than matched non-obese controls.<sup>1</sup> While it is possible, although unproven, that the virtual abolition of plasma ghrelin seen after roux-en-Y gastric bypass surgery may contribute to the paradoxical reduction in hunger



observed in these patients, it is simplistic to suggest that the moderate reduction in ghrelin, as seen in the *H pylori* infected group in this study, is protective against the development of obesity and its associated conditions.

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## Author's reply

Macadam *et al* have rightly questioned whether our novel observation is merely epiphenomenal or of pathophysiological significance. Their "gut feeling" is that it is the former as the changes are "mild" and ghrelin concentrations after *Helicobacter pylori* cure are no different from those seen in a non-obese Western population. They also suggest that the "moderate" reduction of ghrelin in *H pylori* positive subjects (which they attribute to oxyntic gland atrophy) is unlikely to protect these individuals from obesity.

There is no doubt that cure of *H pylori* increases plasma ghrelin in "healthy subjects". The real questions are: whether plasma ghrelin concentrations are higher in *H pylori* negative individuals and, if so, whether the higher ghrelin concentrations cause weight gain, and whether any weight gained exacerbates gastro-oesophageal acid reflux enough to induce Barrett's oesophagus and cancer. There are no satisfactory answers to these questions based on first class evidence but in our discussion, we considered some indirect evidence. Firstly, populations with a high prevalence of *H pylori* have a relatively high proportion of thin children and adults, and those with a low prevalence have a higher proportion of obese individuals; we acknowledge the numerous other confounding factors in our paper.

Secondly, Furuta *et al* showed that patients cured of *H pylori* gained weight.<sup>1</sup> Lane *et al*, continuing their reporting of the large Bristol *Helicobacter* project, showed that at the end of six months, individuals who received treatment for *H pylori* increased their weight by 0.6 kg over and above a matched group that received placebo.<sup>2</sup> Finally, in the only published study of its kind, infusion of ghrelin into healthy subjects was associated with increased appetite and food intake.<sup>3</sup>

In the presence of *H pylori*, abnormalities in the function of the gastric neuroendocrine cell population can be detected long before gastric atrophy occurs. "Inappropriate" hypergastrinaemia and disturbances in D cell function have been described; these are fully reversible, returning to normal soon after *H pylori* cure.<sup>4,5</sup> Similarly, gastric atrophy which is irreversible in the short term is unlikely to be the mechanism that mediates hypo-ghrelinaemia in *H pylori* positive subjects, given that reversion to normal non-obese concentrations occurred 6–12 weeks after

cure, which was the time course of our study. Also, the median age of our subjects was 36 years; the fact that they had normal gastrin concentrations and 24 hour intragastric acidity makes it unlikely that they had significant gastric atrophy.

In general, single factors rarely account for large epidemiological trends. We do not believe that everything can be explained by ghrelin; that would really be simplistic. However, we believe that *H pylori* positive subjects with low ghrelin may have decreased appetite and food intake and are thinner than their *H pylori* negative counterparts in the Western world. Their poor nutritional status would be exaggerated by coexisting dyspepsia due to peptic ulceration, concurrent infection, and poor diet. They would have relatively lower intragastric acidity. Taken together, these factors could protect these individuals from gastro-oesophageal reflux disease (GORD). Conversely, having normal ghrelin, a good appetite, and normal intragastric acidity could make GORD more likely, possibly leading to Barrett's oesophagus and oesophageal adenocarcinoma.

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## CORRECTION

In the paper by Feinle-Bisset *et al* (*Gut* 2003; **52**: 1414–18), an author was missing from the author list, listing only three of the authors as C Feinle-Bisset, B Meier and M Fried. In fact, there was a fourth co-author, C Beglinger, based at University Hospital Basle, Switzerland.

## NOTICES

### British Society of Gastroenterology Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United Kingdom for specialist experience and training in endoscopy.

Specialist registrars who have not achieved their CCST are expected to have the approval

of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applicants are expected to provide confirmation that they have been accepted for training in the unit that they wish to visit.

Successful applicants will be expected to provide a brief written report to the Endoscopy Committee of the outcome of their visit.

Application forms are available from the British Society of Gastroenterology Office, 3 St Andrew's Place, London NW1 4LB. Email: [bsg@mailbox.ulcc.ac.uk](mailto:bsg@mailbox.ulcc.ac.uk)

### Hong Kong-Shanghai International Liver Congress 2004

This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is "Liver Diseases in the Post-Genomic Era". Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: [kristieleung@hepa2004.org](mailto:kristieleung@hepa2004.org); website: [www.hepa2004.org](http://www.hepa2004.org)

### PET/CT and SPECT/CT Imaging in Medical, Radiation, Surgical and Nuclear Oncology

This continuing medical education programme will take place on 19–20 March 2004 at Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. Further details: Office of Continuing Medical Education, Johns Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205-2195. Tel: +1 410 955 2959; fax: +1 410 955 0807; email: [cmenet@jhmi.edu](mailto:cmenet@jhmi.edu); website: [www.hopkinscme.org](http://www.hopkinscme.org)

### 39<sup>th</sup> Annual Meeting of the European Association for the Study of the Liver

This meeting will be held on 15–19 April 2004 in Berlin, Germany. Further details: Secretariat, c/o Kenes International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0488; fax: +41 22 732 2850; email: [info@easl.ch](mailto:info@easl.ch); website: [www.easl.ch/easl2004](http://www.easl.ch/easl2004)

- Deadline for receipt of abstracts: 16 November 2003
- Deadline for early registration 10 February 2004

### 14<sup>th</sup> International Workshop of Digestive Endoscopy, Ultrasonography and Radiology

The 14<sup>th</sup> International Workshop of Digestive Endoscopy, Ultrasonography and Radiology will be held in Marseille on 27–28 May 2004. For further information, please contact: Nathalie Fontant, Atelier Phenix, 41 rue Docteur Morrucci, 13006 — Marseille (tel: (33) 04-91-37-50-83; fax: (33) 04-91-57-15-28; e-mail: [nfontant@aphenix.com](mailto:nfontant@aphenix.com)).

### International Hans Popper Award 2003

This year the International Hans Popper Award goes to Gut editorial board member, Professor Scott Laurence Friedman of the Mount Sinai School of Medicine in New York, for his pioneering work on the pathogenesis of hepatic fibrosis, which ultimately led to the discovery of hepatic stellate cells.